BSKB 703-205-8000
JENSEN et al.
2815-0159P
3063
May 15, 2001

jc997 U.S. PTO
09/854694
05/15/01

Kongeriget Danmark

Patent application No.: PA 1999 00660

Date of filing: 12 May 1999

Applicant: NeuroSearch A/S
Smedeland 26B
DK-2600 Glostrup

This is to certify the correctness of the following information;

The attached photocopy is a true copy of the following document:

- The specification, claims and abstract as filed with the application on the filing date indicated above.

Patent- og Varemærkestyrelsen
Kongeriget Danmark

Patent- og
Varemærkestyrelsen
Erhvervsministeriet

TAASTRUP 27 March 2001

Lizzi Vester

Lizzi Vester
Head of Section

ION CHANNEL MODULATING AGENTS

TECHNICAL FIELD

The present invention relates to ion channel modulating agents. More particularly, the present invention relates to a particular class of chemical compounds that has proven useful as modulators of SK_{Ca}, IK_{Ca} and BK_{Ca} channels. In further aspects, the present invention relates to the use of these SK/IK/BK channel modulating agents for the manufacture of medicaments, and pharmaceutical compositions comprising the SK/IK/BK channel modulating agents.

The SK/IK/BK channel modulating agents of the invention are useful for the treatment or alleviation of diseases and conditions associated with the SK/IK/BK channels.

BACKGROUND ART

Ion channels are transmembrane proteins, which catalyse the transport of inorganic ions across cell membranes. The ion channels participate in processes as diverse as the generation and timing of action potentials, synaptic transmissions, secretion of hormones, contraction of muscles, etc.

Many drugs exert their effects via modulation of ion channels. Examples are anti-epileptic compounds like Phenytoin and Lamotrigine, which block voltage dependent Na^+-channels in the brain, anti-hypertensive drugs like Nifedipine and Diltiazem, which block voltage dependent Ca^{2+}-channels in smooth muscle cells, and stimulators of insulin release like Glibenclamide and Tolbutamide, which block an ATP-regulated K^+-channel in the pancreas.

All mammalian cells express potassium (K^+) channels in their cell membranes, and the channels play a dominant role in the regulation of the membrane potential. In nerve and muscle cells they regulate the frequency and form of the action potential, the release of neurotransmitters, and the degree of broncho- and vasodilation.

From a molecular point of view, the K^+ channels represent the largest and most diverse group of ion channels. For an overview they can be divided into five large

subfamilies: Voltage-activated K^+ channels (K_v), long QT related K^+ channels (KvLQT), inward rectifiers (K_{IR}), two-pore K^+ channels (K_{TP}), and calcium-activated K^+ channels (K_{ca}).

The latter group, the Ca^{2+}-activated K^+ channels, consists of three well-defined subtypes: SK channels, IK channels and BK channels. SK, IK and BK refer to the single-channel conductance (**S**mall, **I**ntermediate and **B**ig conductance **K** channel). The SK, IK, and BK channels exhibit differences in e.g. voltage- and calcium-sensitivity, pharmacology, distribution and function.

Ca^{2+}-activated SK channels are present in many central neurons and ganglia, where their primary function is to hyperpolarize nerve cells following one or several action potentials to prevent long trains of epileptogenic activity to occur. The SK channels are also present in several peripheral cells including skeletal muscle, gland cells, liver cells, and T-lymphocytes.

The significance of SK channels in normal skeletal muscle is not clear, but their number is significantly increased in denervated muscle, and the large number of SK channels in the muscle of patients with myotonic muscle dystrophia suggest a role in the pathogenesis of the disease.

A number of blockers of SK channels exist, e.g. apamin, atracurium, pancuronium, and tubocurarine, and they are all positively charged molecules which act as pore blockers.

The Ca^{2+}-activated IK channel shares a number of characteristics with the Ca^{2+}-activated SK channel, since it is highly K-selective, is activated by sub-micromolar concentrations of Ca^{2+}, and has an inwardly rectifying conductance. However, there are also striking differences. The unit conductance of the IK channel is 4-5 fold higher than that of the SK channel, and the distribution of the IK channel is restricted to the blood and vasculature. Thus, the IK channel is not expressed in the nervous system and in muscle, but in endothelial cells, cells of epithelial origin and in red blood cells.

In the red blood cells, where the IK channel has been denominated the Gardos channel, a rise in the concentration of intracellular Ca^{2+} opens the channel and causes potassium loss and cell dehydration, a condition which is exacerbated in sickle cell anemia. Promising therapeutic approaches for sickle cell anemia involve specific block of the IK channel.

IK channels have also been implicated in the microvasculature of the kidney, where they may be responsible for the vasodilatory effects of bradykinin. The decrease in blood pressure during septic shock is caused by an increased NO production by the endothelial cells, and the IK channels in these cells are responsible for maintaining the Ca^{2+} influx activating the Ca^{2+}-sensitive NO-synthase.

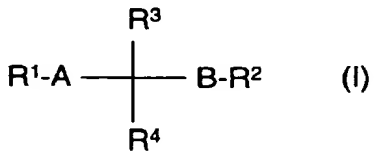
In brain capillary endothelial cells, IK channels, activated by endothelin that is produced by neurons and glia, shunt excess K^+ into the blood. Neurotrophilic granulocytes, i.e. mobile phagocytic cells that defend the body against microbial invaders, undergo large depolarisation subsequent to agonistic stimulation, and IK channels have been implicated in depolarising the stimulated granulocyte.

The Ca^{2+}-activated BK channels present in many cells including most central and peripheral nerve cells, striated muscle cells, cardiac cells, smooth muscle cells of the airways, the vasculature, the gastrointestinal tract and bladder, in endo- and exocrine glands including pancreatic b-cells and in kidney tubules.

SUMMARY OF THE INVENTION

According to the present invention it has now been found that a particular group of chemical compounds possess valuable activity as modulators of SK_{Ca}, IK_{Ca} and/or BK_{Ca} channels.

In its first aspect the invention relates to novel chemical compounds represented by the general formula



(I)

wherein

A and B, independently of each another represent a group of the formula -$(CH_2)_n$-, of the formula -$(CH_2)_n$-Y- (in either direction), or of the formula -$(CH_2)_n$-Y-$(CH_2)_m$-;

in which formulas n and m, independently of each another, represent 0, 1, 2, 3 or 4, and Y represents O, S, or NR'", wherein R'" represents hydrogen or alkyl;

R^1 and R^2, independently of each another, represent alkyl, alkenyl, alkynyl, cycloalkyl, amino, trihalogenmethyl, nitro, cyano, or phenyl, or a group of the formula -

OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', -C(O)NR'(OR"), -C(S)NR'(OR"), -C(O)NR'(SR"), -C(S)NR'(SR"), $-CH(CN)_2$, $-C(O)NR'_2$, $-C(S)NR'_2$, $-CH[C(O)R']_2$, $-CH[C(S)R']_2$, $-CH[C(O)OR']_2$, $-CH[C(S)OR']_2$, $-CH[C(O)SR']_2$, $-CH[C(S)SR']_2$, CH_2OR', or CH_2SR'; a partially or completely saturated mono- or polycyclic group, a mono- or poly-heterocyclic group, an aralkyl group, or a hetero-alkyl group, which mono- or polycyclic groups or aralkyl or hetero-alkyl groups may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR', or a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR"'R"", wherein R"' and R"", independently of each another, represent hydrogen or alkyl;

R^3 and R^4, independently of each another, represent alkyl, alkenyl, alkynyl, cycloalkyl, amino, trihalogenmethyl, nitro, cyano, or phenyl, or a group of the formula -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', -C(O)NR'(OR"), -C(S)NR'(OR"), -C(O)NR'(SR"), -C(S)NR'(SR"), $-CH(CN)_2$, $-C(O)NR'_2$, $-C(S)NR'_2$, $-CH[C(O)R']_2$, $-CH[C(S)R']_2$, $-CH[C(O)OR']_2$, $-CH[C(S)OR']_2$, $-CH[C(O)SR']_2$, $-CH[C(S)SR']_2$, CH_2OR', or CH_2SR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR"'R"", wherein R"' and R"", independently of each another, represent hydrogen or alkyl;

or R^3 and R^4 together form a partially or completely saturated mono- or polycyclic group, or a mono- or poly-heterocyclic group, which mono- or polycyclic groups may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR', or a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times

with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR'', -R'SR'', -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

wherein R' and R'', independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR'''R'''', wherein R''' and R'''', independently of each another, represent hydrogen or alkyl.

In a second aspect, the invention provides a pharmaceutical composition comprising a chemical compound of the invention for the treatment or alleviation of diseases or conditions responsive to modulation of SK_{Ca}, IK_{Ca} and/or BK_{Ca} channels.

The SK/IK/BK channel modulating agents of the invention are useful for the treatment or alleviation of diseases or conditions responsive to modulation of SK_{Ca}, IK_{Ca} and/or BK_{Ca} channels.

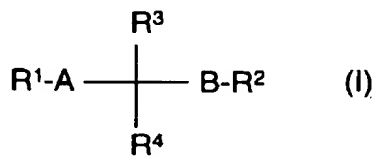
DETAILED DISCLOSURE OF THE INVENTION

According to the present invention it has now been found that a particular group of chemical compounds possess valuable activity as modulators of Sk_{Ca}, IK_{Ca} and/or BK_{Ca} channels.

SK/IK/BK Modulating Agents

In the context of this invention, chemical compounds capable of affecting Sk_{Ca}, IK_{Ca} and/or BK_{Ca} channels are designated SK/IK/BK channel modulating agents. The SK/IK/BK channel modulating agents of the invention may affect the ion channels by opening (activating) the channels or by inhibiting (blocking) the channels.

The SK/IK/BK channel modulating agents of the invention are represented by the following general formula



(I)

and a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

A and B, independently of each another represent a group of the formula -$(CH_2)_n$-, of the formula -$(CH_2)_n$-Y- (in either direction), or of the formula -$(CH_2)_n$-Y-$(CH_2)_m$-;

in which formulas n and m, independently of each another, represent 0, 1, 2, 3 or 4, and Y represents O, S, or NR'", wherein R'" represents hydrogen or alkyl;

R^1 and R^2, independently of each another, represent

alkyl, alkenyl, alkynyl, cycloalkyl, amino, trihalogenmethyl, nitro, cyano, or phenyl, or a group of the formula -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', -C(O)NR'(OR"), -C(S)NR'(OR"), -C(O)NR'(SR"), -C(S)NR'(SR"), -$CH(CN)_2$, -C(O)NR'_2, -C(S)NR'_2, -$CH[C(O)R']_2$, -$CH[C(S)R']_2$, -$CH[C(O)OR']_2$, -$CH[C(S)OR']_2$, -$CH[C(O)SR']_2$, -$CH[C(S)SR']_2$, CH_2OR', or CH_2SR';

a partially or completely saturated mono- or polycyclic group, a mono- or poly-heterocyclic group, an aralkyl group, or a hetero-alkyl group, which mono- or polycyclic groups or aralkyl or hetero-alkyl groups may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR', or a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or alkyl;

R^3 and R^4, independently of each another, represent

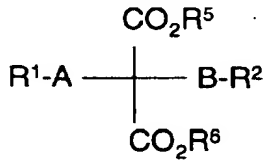
alkyl, alkenyl, alkynyl, cycloalkyl, amino, trihalogenmethyl, nitro, cyano, or phenyl, or a group of the formula -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', -C(O)NR'(OR"), -C(S)NR'(OR"), -C(O)NR'(SR"), -C(S)NR'(SR"), -$CH(CN)_2$, -C(O)NR'_2, -C(S)NR'_2, -$CH[C(O)R']_2$, -$CH[C(S)R']_2$, -$CH[C(O)OR']_2$, -$CH[C(S)OR']_2$, -$CH[C(O)SR']_2$, -$CH[C(S)SR']_2$, CH_2OR', or CH_2SR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or alkyl;

or R^3 and R^4 together form a partially or completely saturated mono- or polycyclic group, or a mono- or poly-heterocyclic group, which mono- or polycyclic groups may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR', or a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or alkyl.

In a preferred embodiment, the chemical compound of the invention is a malonic acid ester derivative of general formula



(II)

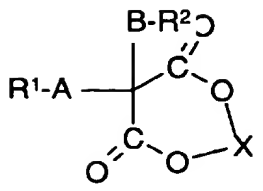
and a pharmaceutically acceptable salt or an oxide or a hydrate thereof,

wherein,

A, B, R^1 and R^2 are as defined above; and

R^5 and R^6, independently of each another, represent hydrogen, alkyl, cycloalkyl, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or alkyl.

In another preferred embodiment, the chemical compound of the invention is a malonic acid ester derivative as described above, in which R^5 and R^6 together form a heterocyclic 6-9 membered ring to give a diester derivative of the general formula



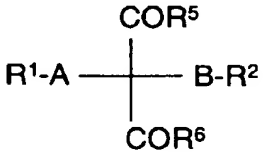
(III)

and a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

A, B, R^1 and R^2 are as defined above; and

X represents a saturated or unsaturated carbon chain of the formula $-(CH_2)_n-$, wherein n is 1, 2, 3 or 4; of the formula $-CH_2-CH=CH-CH_2-$; of the formula $-CH=CH-CH_2-CH_2-$ (in either direction); or of the formula $-CH_2-C\equiv C-CH_2-$.

In a third preferred embodiment, the chemical compound of the invention is an oxo derivative of the general formula



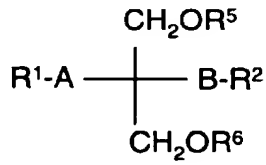
(IV)

and a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

A, B, R^1 and R^2 are as defined above; and

R^5 and R^6, independently of each another, represent hydrogen, alkyl, cycloalkyl, or a group of the formula NR'''R'''', wherein R''' and R'''', independently of each another, represent hydrogen or alkyl.

In a fourth preferred embodiment, the chemical compound of the invention is an ether derivative of the general formula



(V)

and a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

A, B, R^1 and R^2 are as defined above; and

R^5 and R^6, independently of each another, represent hydrogen, alkyl, cycloalkyl, or a group of the formula NR'''R'''', wherein R''' and R'''', independently of each another, represent hydrogen or alkyl.

In a more preferred embodiment, the chemical compound of the invention is a chemical compound as defined above, wherein R^1 and R^2 independently of each another represents an alkyl group; a phenyl or a benzyl group, which phenyl and benzyl groups may optionally be substituted one or more times with substituent selected from the group consisting of halogen, CF_3, CN, amino or nitro; a mono-heterocyclic group, which heterocyclic group may optionally be substituted one or more times with substituent selected from the group consisting of halogen, CF_3, CN, amino or nitro; a heteroalkyl group, wherein the heterocyclic group a mono-heterocyclic group, which heterocyclic group may optionally be substituted one or more times with substituent selected from the group consisting of halogen, CF_3, CN, amino or nitro.

In another preferred embodiment, the chemical compound of the invention is a chemical compound as defined above, wherein R^1 and R^2 independently of each another represents phenyl, 1-, 2 or 3-chlorophenyl, 1-, 2- or 3-chlorobenzyl, 1-, 2- or 3-nitrophenyl, 1-, 2- or 3-nitrobenzyl, 1-, 2 or 3-trifluoromethylphenyl, 1-, 2- or 3-trifluoromethylbenzyl, or 1-nitro-3-trifluoromethyl-5-chlorophenyl, 1-nitro-3-trifluoromethyl-5-chlorobenzyl.

In a third preferred embodiment, the chemical compound of the invention is a chemical compound as defined above, wherein mono-heterocyclic group is an aromatic heterocyclic monocyclic group, in particular 1,3,2,4- or 1,3,4,5-dioxadiazolyl, dioxatriazinyl, dioxazinyl, 1,2,3-, 1,2,4-, 1,3,2- or 1,3,4-dioxazolyl, 1,3,2,4- or 1,3,4,5-dithiadiazolyl, dithiatriazinyl, dithiazinyl, 1,2,3-dithiazolyl, furanyl, furazanyl, imidazolyl, isoimidazolyl, 2-isoimidazolyl, isoindazolyl, isothiazolyl, isoxazolyl, 1,2,3-, 1,2,4-, 1,2,5- or 1,3,4-oxadiazolyl, oxatetrazinyl, oxatriazinyl, 1,2,3,4- or 1,2,3,5-oxatriazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl (azolyl), 1,2,3,4- or 2,1,3,4-tetrazolyl, thiadiazolyl, thiazolyl, thienyl, 1,2,3-, 1,2,4- or 1,3,5-triazinyl, or 1,2,3-, 1,2,4-, 2,1,3- or 4,1,2-triazolyl.

In a fourth preferred embodiment, the chemical compound of the invention is a chemical compound as defined above, wherein the mono-heterocyclic group is 2-furanyl, 3-furanyl, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isoxazolyl, 1-, 2- or 3-pyridinyl, or 1- or 2-thienyl.

In a fifth preferred embodiment, the chemical compound of the invention is a chemical compound as defined above, wherein the mono-heterocyclic group is 4-(3,5-dimethyl)-isoxazolyl.

In a sixth preferred embodiment, the chemical compound of the invention is a chemical compound as defined above, wherein the mono-heterocyclic group is a saturated or partially saturated heterocyclic monocyclic group, in particular 1,3,5,6,2-dioxadiazinyl, 1,2,3,4,5-, 1,2,3,5,4-dioxadiazolyl, dioxanyl, 1,3-dioxolyl, 1,3,5,6,2-dithiadiazinyl, 1,2,3,4,5- or 1,2,3,5,4-dithiadiazolyl, 2-isoimidazolyl, isopyrrolyl, isotetrazolyl, 1,2,3- or 1,2,4-isotriazolyl, morpholinyl, oxadiazinyl, 1,2,4-, 1,2,6-, 1,3,2-, 1,3,6- or 1,4,2-oxazinyl, piperazinyl, piperidinyl, 1,2-, 1,3- or 1,4-pyranyl, or pyrrolidinyl.

In a seventh preferred embodiment, the chemical compound of the invention is a chemical compound as defined above, wherein the mono-heterocyclic group is an aromatic heterocyclic polycyclic group, in particular acridinyl, benzimidazolyl, 1,2- or 1,4-benzisothiazinyl, 1,2- or 1,4-benzisoxazinyl, benzisoxazole, benzothiazolyl, benzofuranyl, isobenzofuranyl, 2,3-benzopyronyl, 1,2,3,4-benzotetrazinyl, 1,3,4,6-benzotetrazolyl, benzothiazolyl, 1,2,3- or 1,2,4-benzotriazinyl, 1,2,3- or 2,1,3-benzotriazolyl, benzoxadiazolyl, benzoxazolyl, carbazolyl, cinnolinyl, coumarinyl, indazolyl, indolyl, isoindolyl, indolizinyl, purinyl, phenazinyl, phenothiazinyl, phenanthridinyl, phthalazinyl, pteridinyl, quinolinyl, quinoxalinyl, isoquinolinyl, quinazolinyl, quinolizinyl, or xanthrenyl.

In an eight preferred embodiment, the chemical compound of the invention is a chemical compound as defined above, wherein the mono-heterocyclic group is a saturated or partially saturated heterocyclic polycyclic group, in particular 1,3-benzisodiazolyl, benzomorpholinyl, 1,2- or 1,4-benzopyranyl, 1,3,2-, 1,4,2-, 2,3,1- or 3,1,4-benzoxazinyl, chromanyl, 4H-chromenyl, or indanyl.

In a ninth preferred embodiment, the chemical compound of the invention is a chemical compound as defined above, wherein the heteroalkyl group is furfuryl, or picolyl.

In a most preferred embodiment, the chemical compound of the invention is

Diethyl 2-(4-fluorophenyl)-2-(3-picolyl)malonate;

Diethyl 2-(4-nitrophenyl)-2-(2-picolyl)malonate;

Diethyl 2-(4-nitrophenyl)-2-(4-picolyl)malonate;

Diethyl 2-phenyl-2-(3-picolyl)malonate;

Diethyl 2-(5-chloro-2-nitro-4-(trifluoromethyl)phenyl)-2-(3-picolyl)malonate;

Diethyl 2-benzyl-2-(3-picolyl)malonate;

Diethyl 2-(4-nitrophenyl)-2-[(benzotriazol-1-yl)methyl]malonate;

Diethyl 2-(2-thienyl)-2-(2-picolyl)malonate;

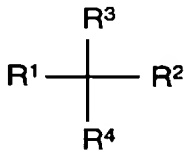
Diethyl 2-(4-(acetylamino)phenyl)-2-(2-picolyl)malonate;

Diethyl 2-(4-(benzoylamino)phenyl)-2-(2-picolyl)malonate; or

2-(4-nitrophenyl)-2-(2-picolyl)malononitril;

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

In another embodiment, the chemical compound of the invention is a represented by the general formula



(VI)

and a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

R^1 and R^2, independently of each another, represent

a partially or completely saturated mono- or polycyclic group, a mono- or poly-heterocyclic group, an aralkyl group, or a hetero-alkyl group, which mono- or polycyclic groups or aralkyl or hetero-alkyl groups may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR', or a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

wherein

R' represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR"'R"", wherein R"' and R"", independently of each another, represent hydrogen or alkyl; and

R^3 and R^4, independently of each another, represent

alkyl, alkenyl, alkynyl, cycloalkyl, amino, trihalogenmethyl, nitro, cyano, or phenyl, or a group of the formula -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', -C(O)NR'(OR"), -C(S)NR'(OR"), -C(O)NR'(SR"), -C(S)NR'(SR"), $-CH(CN)_2$, $-C(O)NR'_2$, $-C(S)NR'_2$, $-CH[C(O)R']_2$, $-CH[C(S)R']_2$, $-CH[C(O)OR']_2$, $-CH[C(S)OR']_2$, $-CH[C(O)SR']_2$, $-CH[C(S)SR']_2$, CH_2OR', or CH_2SR';

wherein

R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or alkyl;

or R^3 and R^4 together form a partially or completely saturated mono- or polycyclic group, or a mono- or poly-heterocyclic group, which mono- or polycyclic groups may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR', or a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

wherein

R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or alkyl.

In more preferred embodiment, the chemical compound of the invention is represented by the general formula VI, wherein

R^1 represents a phenyl group, which may optionally be substituted one or more times with substituents selected from the group consisting of

halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR', or

a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or alkyl;

R^2 represents alkyl, alkenyl, alkynyl, cycloalkyl, amino, trihalogenmethyl, nitro, cyano, or phenyl, or a group of the formula -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', -C(O)NR'(OR"), -C(S)NR'(OR"), -C(O)NR'(SR"), -C(S)NR'(SR"), $-CH(CN)_2$, $-C(O)NR'_2$, $-C(S)NR'_2$, $-CH[C(O)R']_2$, $-CH[C(S)R']_2$, $-CH[C(O)OR']_2$, $-CH[C(S)OR']_2$, $-CH[C(O)SR']_2$, $-CH[C(S)SR']_2$, CH_2OR', or CH_2SR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or alkyl;

R^3 and R^4, independent of each another, represent alkyl, alkenyl, alkynyl, cycloalkyl, amino, trihalogenmethyl, nitro, cyano, or phenyl, or a group of the formula -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', -C(O)NR'(OR"), -C(S)NR'(OR"), -C(O)NR'(SR"), -C(S)NR'(SR"), $-CH(CN)_2$, $-C(O)NR'_2$, $-C(S)NR'_2$, $-CH[C(O)R']_2$, $-CH[C(S)R']_2$, $-CH[C(O)OR']_2$, $-CH[C(S)OR']_2$, $-CH[C(O)SR']_2$, $-CH[C(S)SR']_2$, CH_2OR', or CH_2SR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or alkyl;

or R^3 and R^4 together form a partially or completely saturated mono- or polycyclic group, or a mono- or poly-heterocyclic group, which mono- or polycyclic groups may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR', or a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times

with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR"'R"", wherein R"' and R"", independently of each another, represent hydrogen or alkyl.

In another preferred embodiment, the chemical compound of the invention is represented by the general formula VI, wherein

R^1 represents a phenyl group, which may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -R'OR", -C(O)R', -C(O)OR', or

a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -R'OR", -C(O)R', or -C(O)OR';

wherein R' and R", independently of each another, represent hydrogen, or alkyl;

R^2 represents alkyl, cycloalkyl, amino, trihalogenmethyl, nitro, or cyano, or a group of the formula -OR', -R'OR", -C(O)R', -C(O)OR', or CH_2OR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, cycloalkyl or alkoxy;

R^3 and R^4, independent of each another, represent alkyl, cycloalkyl, amino, trihalogenmethyl, nitro, cyano, or phenyl, or a group of the formula -OR', -R'OR", -C(O)R', -C(O)OR', or CH_2OR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, cycloalkyl or alkoxy.

In a third preferred embodiment, the chemical compound of the invention is represented by the general formula VI, wherein

R^1 represents

a phenyl group, which may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl,

amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -R'OR", -C(O)R', -C(O)OR', or

a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -R'OR", -C(O)R', or -C(O)OR';

wherein R' and R", independently of each another, represent hydrogen, or alkyl;

R^2 represents alkyl, cycloalkyl, amino, trihalogenmethyl, nitro, or cyano, or a group of the formula -OR', -R'OR", -C(O)R', -C(O)OR', or CH_2OR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, cycloalkyl or alkoxy;

R^3 and R^4 together form a partially or completely saturated mono- or polycyclic group, which mono- or polycyclic groups may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -R'OR", -C(O)R', -C(O)OR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, cycloalkyl or alkoxy.

In a most preferred embodiment, the chemical compound of the invention represented by the general formula VI is

2-(3-Phenoxyphenyl)butyronitrile;

2-(2-Chlorophenyl)butyronitrile;

Dicyclopropan(4-chlorophenyl)carbinol;

Ethyl 1-(4-chlorophenyl)cyclopentane-1-carboxylate; or

1-(4-Chlorophenyl)-1-(3-methyl-5-oxadiazolyl)cyclopentane;

or a pharmaceutically acceptable salt or an oxide or a hydrate hereof.

Definition of Substituents

In the context of this invention halogen represents a fluorine, a chlorine, a bromine or an iodine atom. Thus, a trihalogenmethyl group represents e.g. a trifluoromethyl group and a trichloromethyl group.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to eighteen carbon atoms (C_{1-18}-alkyl), more preferred of from one to six carbon atoms (C_{1-6}-alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C_{1-4}-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In a preferred embodiment of this invention alkyl represents a C_{1-3}-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C_{3-7}-cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

In the context of this invention an alkenyl group designates a carbon chain containing one or more double bonds, including di-enes, tri-enes and poly-enes. In a preferred embodiment the alkenyl group of the invention comprises of from two to six carbon atoms (C_{2-6}-alkenyl), including at least one double bond. In a most preferred embodiment the alkenyl group of the invention is ethenyl; 1,2- or 2,3-propenyl; or 1,2-, 2,3-, or 3,4-butenyl.

In the context of this invention an alkynyl group designates a carbon chain containing one or more triple bonds, including di-ynes, tri-ynes and poly-ynes. In a preferred embodiment the alkynyl group of the invention comprises of from two to six carbon atoms (C_{2-6}-alkynyl), including at least one triple bond. In its most preferred embodiment the alkynyl group of the invention is ethynyl, 1,2- or 2,3-propynyl, 1,2-, 2,3- or 3,4-butynyl.

In the context of this invention an alkoxy group designates an "alkyl-O-" group, wherein alkyl is as defined above.

In the context of this invention an acyl group designates a carboxy group (-COOH) or an alkylcarbonyl group (alkyl-CO-), wherein alkyl is as defined above. Examples of preferred acyl groups of the invention include carboxy, acetyl, and propionyl.

In the context of this invention an amido group designates a substituent of the formula R'-CO-NH- or R'-CO-N(alkyl)-, wherein R' represents hydrogen or an alkyl group as defined above. Examples of preferred amido groups include formamido, acetamido, and propionamido.

In the context of this invention an amino group may be a primary ($-NH_2$), secondary (-NH-alkyl), or tertiary ($-N(alkyl)_2$) amino group, i.e. it may be substituted once or twice with an alkyl group as defined above.

In the context of this invention a mono- or polycyclic aryl group designates a monocyclic or polycyclic aromatic hydrocarbon group. Examples of preferred aryl groups of the invention include phenyl, naphthyl and anthracenyl.

In the context of this invention a partially or completely saturated mono- or polycyclic group designates mono- or polycyclic aryl group, i.e. monocyclic or polycyclic aromatic hydrocarbon groups. Examples of preferred partially saturated monocyclic groups include cyclopenta-2,4-diene-1-ylidene.

In the context of this invention an aralkyl group designates an aryl group as defined above, which aryl group is attached to an alkyl group as also defined above. Examples of preferred aralkyl groups of the invention include benzyl.

In the context of this invention a mono- or poly-heterocyclic group is a mono- or polycyclic compound, which holds one or more heteroatoms in its ring structure. Preferred heteroatoms include nitrogen (N), oxygen (O), and sulphur (S). One or more of the ring structures may in particular be aromatic (i.e. a heteroaryl), saturated or partially saturated. Preferred heterocyclic monocyclic groups of the invention include 5- and 6-membered heterocyclic monocyclic groups.

Examples of preferred aromatic heterocyclic monocyclic groups of the invention include 1,3,2,4- or 1,3,4,5-dioxadiazolyl, dioxatriazinyl, dioxazinyl, 1,2,3-, 1,2,4-, 1,3,2- or 1,3,4-dioxazolyl, 1,3,2,4- or 1,3,4,5-dithiadiazolyl, dithiatriazinyl, dithiazinyl, 1,2,3-dithiazolyl, furanyl, furazanyl, imidazolyl, isoimidazolyl, 2-isoimidazolyl, isoindazolyl, isothiazolyl, isoxazolyl, 1,2,3-, 1,2,4-, 1,2,5- or 1,3,4-oxadiazolyl, oxatetrazinyl, oxatriazinyl, 1,2,3,4- or 1,2,3,5-oxatriazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl (azolyl), 1,2,3,4- or 2,1,3,4-tetrazolyl, thiadiazolyl, thiazolyl, thienyl, 1,2,3-, 1,2,4- or 1,3,5-triazinyl, and 1,2,3-, 1,2,4-, 2,1,3- or 4,1,2-triazolyl. Most preferred heterocyclic monocyclic groups of the invention include furan-2-yl, furan-3-yl, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isoxazolyl, 1-, 2- or 3-pyridinyl, and 1- or 2-thienyl.

Examples of preferred saturated or partially saturated heterocyclic monocyclic groups of the invention include 1,3,5,6,2-dioxadiazinyl, 1,2,3,4,5-, 1,2,3,5,4-dioxadiazolyl, dioxanyl, 1,3-dioxolyl, 1,3,5,6,2-dithiadiazinyl, 1,2,3,4,5- or

1,2,3,5,4-dithiadiazolyl, 2-isoimidazolyl, isopyrrolyl, isotetrazolyl, 1,2,3- or 1,2,4-isotriazolyl, morpholinyl, oxadiazinyl, 1,2,4-, 1,2,6-, 1,3,2-, 1,3,6- or 1,4,2-oxazinyl, piperazinyl, piperidinyl, 1,2-, 1,3- or 1,4-pyranyl, and pyrrolidinyl.

Examples of preferred aromatic heterocyclic polycyclic groups of the invention include acridinyl, benzimidazolyl, 1,2- or 1,4-benzisothiazinyl, 1,2- or 1,4-benzisoxazinyl, benzisoxazole, benzothiazolyl, benzofuranyl, isobenzofuranyl, 2,3-benzopyronyl, 1,2,3,4-benzotetrazinyl, 1,3,4,6-benzotetrazolyl, benzothiazolyl, 1,2,3- or 1,2,4-benzotriazinyl, 1,2,3- or 2,1,3-benzotriazolyl, benzoxadiazolyl, benzoxazolyl, carbazolyl, cinnolinyl, coumarinyl, indazolyl, indolyl, isoindolyl, indolizinyl, purinyl, phenazinyl, phenothiazinyl, phenanthridinyl, phthalazinyl, pteridinyl, quinolinyl, quinoxalinyl, isoquinolinyl, quinazolinyl, quinolizinyl, and xanthrenyl.

Examples of preferred saturated or partially saturated heterocyclic polycyclic groups of the invention include 1,3-benzisodiazolyl, benzomorpholinyl, 1,2- or 1,4-benzopyranyl, 1,3,2-, 1,4,2-, 2,3,1- or 3,1,4-benzoxazinyl, chromanyl, 4H-chromenyl, and indanyl.

In the context of this invention a hetero-alkyl group designates a mono- or poly-heterocyclic group as described above, which heterocyclic group is attached to an alkyl group as also defined above. Examples of preferred hetero-alkyl groups of the invention include furfuryl and picolyl.

Pharmaceutically Acceptable Salts

The SK/IK/BK channel modulating agents of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulfonate derived from benzensulfonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the formate derived from formic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from

glycolic acid, the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulfonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the sulphate derived from sulphuric acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

Metal salts of a chemical compound of the invention includes alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.

The chemical compound of the invention may be provided in unsolved or solvated forms together with a pharmaceutically acceptable solvents such as water, ethanol, and the like. Solvated forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, solvated forms are considered equivalent to unsolved forms for the purposes of this invention.

Steric Isomers

The SK/IK/BK channel modulating agents of the present invention may exist in (+) and (-) forms as well as in racemic forms. The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by

treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Biological Activity

According to the present invention it has now been found that the isatin derivatives of the invention possess valuable activity as modulators of SK_{Ca}, IK_{Ca} and/or BK_{Ca} channels.

The SK/IK/BK channel modulating activity may be monitored using conventional electrophysiological methods such as patch-clamp techniques, or conventional spectroscopic methods such as FLIPR assay (Fluorescence Image Plate Reader; available from Molecular Devices). These methods generally comprises subjecting an SK_{Ca}, IK_{Ca} or BK_{Ca} containing cell to the action of the chemical compound of the invention, followed by monitoring the membrane potential of the SK_{Ca}, IK_{Ca} or BK_{Ca} containing cell in order to identify changes in the membrane potential caused by the action of the compound of the invention.

In Example 9 the biological activity of the compounds of the invention is demonstrated using electrophysiologic patch-clamp techniques.

Based on their biological activity the compounds of the invention are considered useful for the treatment or alleviation of diseases or conditions responsive to modulation of SK_{Ca}, IK_{Ca} and/or BK channels, including diseases or conditions like respiratory diseases such as asthma, cystic fibrosis, chronic obstructive pulmonary

disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic hearth disease, angina pectoris, coronary hearth disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.

The compounds of the invention is considered particularly useful for reducing or inhibiting undesired immune-regulatory actions. In a preferred embodiment, therefore, the compounds of the may be used in the treatment or alleviation of a diseases, disorders or condition related to immune dysfunction, or in order to obtain immune suppression in an individual in need herefore.

In a more preferred embodiment, the invention relates to the use of an IK_{Ca} inhibitory compound of the invention in a combination therapy with known immune-suppressants for the treatment or alleviation of a diseases, disorders or condition related to immune dysfunction, or for obtaining immune suppression. Preferred immune-suppressants to combine with the compounds of the invention include Amphotericin, Busulphan, Co-trimoxazole, Chlorambucil, colony stimulating factors, corticosteroids, Cyclophosphamide, Fluconazole, folinic acid, Ganciclovir, antilymphocyte immunoglobulins, normal immunoglobulins, Methotrexate, Methylprednisolone, Octreotide, Oxpentifylline, Tacrolimus, Thalidomide, Zolimomab aritox, and the calcineurin inhibitors (protein phosphatase 2B inhibitors), in particular Cyclosporin, FK506 (?), ... andre ...?

Conditions which may benefit from this treatment include, but are not limited to diseases, disorders or conditions such as auto-immune diseases, e.g. Addison's disease, alopecia areata, Ankylosing spondylitis, haemolytic anemia (anemia haemolytica), pernicious anemia (anemia perniciosa), aphthae, aphthous stomatitis, arthritis, arteriosclerotic disorders, osteoarthritis, rheumatoid arthritis, aspermiogenese, asthma bronchiale, auto-immune asthma, auto-immune hemolysis, Bechet's disease, Boeck's disease, inflammatory bowel disease, Burkitt's lymphoma, Chron's disease,

chorioiditis, colitis ulcerosa, Coeliac disease, cryoglobulinemia, dermatitis herpetiformis, dermatomyositis, insulin-dependent type I diabetes, juvenile diabetes, idiopathic diabetes insipidus, insulin-dependent diabetes mellisis, auto-immune demyelinating diseases, Dupuytren's contracture, encephalomyelitis, encephalomyelitis allergica, endophthalmia phacoanaphylactica, enteritis allergica, auto-immune enteropathy syndrome, erythema nodosum leprosum, idiopathic facial paralysis, chronic fatigue syndrome, febris rheumatica, glomerulo nephritis, Goodpasture's syndrome, Graves' disease, Hamman-Rich's disease, Hashimoto's disease, Hashimoto's thyroiditis, sudden hearing loss, sensoneural hearing loss, hepatitis chronica, Hodgkin's disease, haemoglobinuria paroxysmatica, hypogonadism, ileitis regionalis, iritis, leucopenia, leucemia, lupus erythematosus disseminatus, systemic lupus erythematosus, cutaneous lupus erythematosus, lymphogranuloma malignum, mononucleosis infectiosa, myasthenia gravis, traverse myelitis, primary idiopathic myxedema, nephrosis, ophthalmia symphatica, orchitis granulomatosa, pancreatitis, pemphigus, pemphigus vulgaris, polyarteritis nodosa, polyarthritis chronica primaria, polymyositis, polyradiculitis acuta, psoreasis, purpura, pyoderma gangrenosum, Quervain's thyreoiditis, Reiter's syndrome, sarcoidosis, ataxic sclerosis, progressive systemic sclerosis, scleritis, sclerodermia, multiple sclerosis, sclerosis disseminata, acquired spenic atrophy, infertility due to antispermatozoan antobodies, thrombocytopenia, idiopathic thrombocytopenia purpura, thymoma, acute anterior uveitis, vitiligo, AIDS, HIV, SCID and Epstein Barr virus associated diseases such as Sjorgren's syndrome, virus (AIDS or EBV) associated B cell lymphoma, parasitic diseases such as Lesihmania, and immune-suppressed disease states such as viral infections following allograft transplantations, graft vs. Host syndrome, transplant rejection, or AIDS, cancers, chronic active hepatitis diabetes, toxic chock syndrome, food poisoning, and transplant rejection.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of a chemical compound having SK_{Ca}, IK_{Ca} or BK_{Ca} modulating activity.

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the

active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the SK/IK/BK channel modulating agents of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefor, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route which suite the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition may be prepared by the skilled person using standard and conventional techniques appropriate to the desired formulation.

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

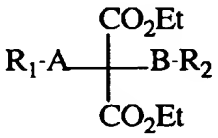
A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg i.v., and from about 1 µg/kg to about 100 mg/kg p.o.

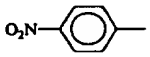
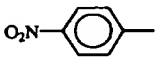
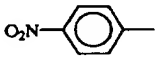
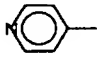
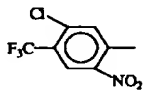
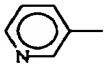
EXAMPLES

The invention is further illustrated with reference to the following examples which are not intended to be in any way limiting to the scope of the invention as claimed.

Table 1

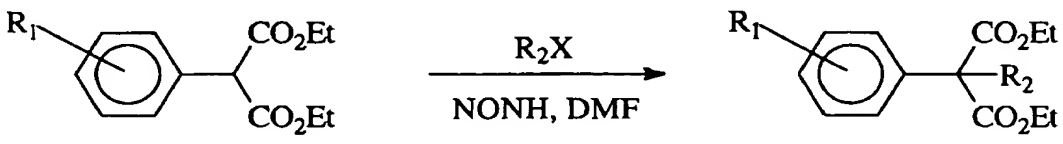
Substituted malonic acid esters



entry	A	B	R_1	R_2	Mp.	Examples
1a	-	CH_2			159-61.5*	1, 2
1b	-	CH_2			161-3*	1, 2
1c	-	CH_2			174-6*	1, 2
1d	-	CH_2	Ph		oil	1, 2
1e	-	CH_2			167-8*	1, 2
1f	CH_2	CH_2	Ph		oil	1, 2
1g	-	CH_2	Ph	OH	oil	3
1h	-	CH_2	Ph	Oac	oil	4

*as the hydrochloride.

Example 1



Diethyl 2-(4-fluorophenyl)-2-(3-picolyl)malonate (**1a**). To a solution of diethyl 2-(4-fluorophenyl)malonate (1 g; 3.6 mmol) in anhydrous DMF (10 ml) was added sodium hydride (4.3 mmol, 0.17 g, 60% dispersion in mineral oil). When the evolution of hydrogen had ceased a solution of 3-picolylchloride* (3.6 mmol) in anhydrous DMF (3 ml) was added and the mixture was heated to 80°C overnight. After cooling four volumes of water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulphate and concentrated under reduced pressure. The concentrate was subjected to chromatography on silica gel using a mixture of ethyl acetate and ligroin (1:1) as the eluent. The product precipitated from the eluate as the hydrochloride upon addition of ethereal hydrogen chloride. Yield: 0.32 g (22%). Mp. 159-161.5°C.

*3-Picolylchloride was prepared immediately prior to use by liberation from the hydrochloride: 3-picolylchloride, hydrochloride (0.58 g; 3.6 mmol) was dissolved in water (5 ml). Ethyl acetate and saturated aqueous sodium carbonate was added and the phases were separated. The aqueous phase was extracted twice with ethyl acetate and the combined organic phases were dried over sodium sulphate and evaporated to dryness. This residue was dissolved in DMF and used as described above.

The following compounds were prepared analogously:

Diethyl 2-(4-nitrophenyl)-2-(2-picolyl)malonate (**1b**) from diethyl 2-(4-nitrophenyl)malonate and 2-picolylchloride. Yield: 34%. Mp. 161-163°C.

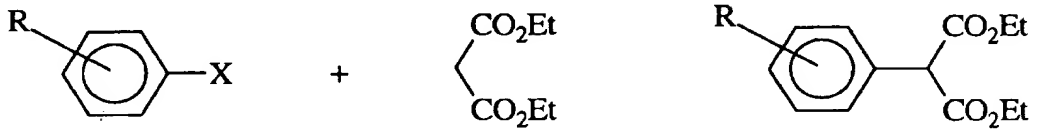
Diethyl 2-(4-nitrophenyl)-2-(4-picolyl)malonate (**1c**) from diethyl 2-(4-nitrophenyl)malonate and 4-picolylchloride. Yield: 23%. Mp. 174-176°C.

Diethyl 2-phenyl-2-(3-picolyl)malonate (**1d**) from diethyl 2-phenylmalonate and 3-picolylchloride. Yield: 58%. M/z: 327 (100%), 281 (43%), 254 (42%), 253 (42%), 235 (51%), 161 (73%).

Diethyl 2-(5-chloro-2-nitro-4-(trifluoromethyl)phenyl)-2-(3-picolyl)malonate (**1e**) from diethyl 2-(5-chloro-2-nitro-4-(trifluoromethyl)phenyl)malonate and 3-picolylchloride. Yield: 11%. Mp. 167-168°C.

Diethyl 2-benzyl-2-(3-picolyl)malonate (**1f**) from diethyl 2-benzylmalonate and 3-picolyl. Yield: 55% (isolated as the free base). Mp. oil.

Example 2

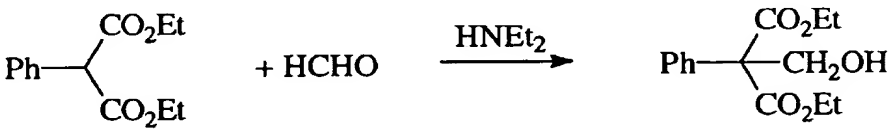


Diethyl 2-(4-nitrophenyl)malonate. To a solution of diethyl malonate (6.1 ml; 40 mmol) in anhydrous THF (60 ml) was added sodium hydride (40 mmol, 1.6 g, 60% dispersion in mineral oil). When the evolution of hydrogen had ceased 1-fluoro-4-nitrobenzene (3.9 ml; 36.3 mmol) was added and the mixture was heated to reflux overnight. The solvent was removed under reduced pressure and the residue was suspended in ethyl acetate. Hydrochloric acid (1 M) was added. The phases were separated and the organic phase was dried over sodium sulphate and evaporated to dryness. The residue was triturated with petroleum ether to afford the product as yellow crystals. Yield: 2.44 g (22%).

The following compound was prepared analogously:

Diethyl 2-(5-chloro-2-nitro-4-trifluoromethylphenyl)malonate from 2,4-dichloro-5-nitrobenzotrifluoride diethyl malonate. Yield: 54%.

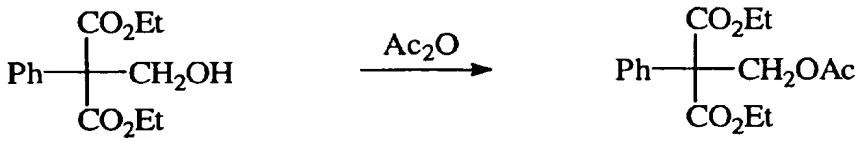
Example 3



Diethyl 2-phenyl-2-(hydroxymethyl)malonate (**1g**). To a solution of diethyl 2-phenylmalonate (20 g; 84.6 mmol) and 37% formaline (200 ml) was added diethylamine (8.12 ml; 116 mmol) dropwise at 0°C. The solution was then allowed to stir at ambient temperature for 3 days. The obtained solution was extracted with diethyl ether. The combined organic phases were washed with water, saturated aqueous NaCl-solution, dried over $MgSO_4$, filtered and evaporated. After column

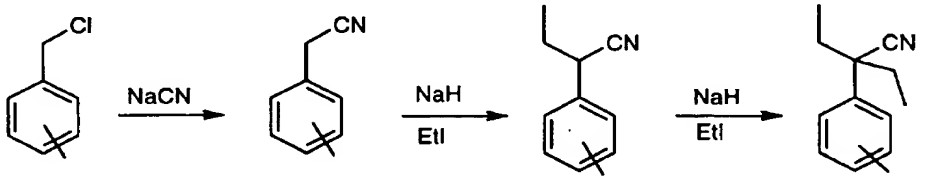
chromatography on silica gel eluting first with benzine (80-100°C) ethyl acetate 6:1, then 3:1, the product was obtained as a slightly yellowish oil (20.1 g, 89%).
^{13}C nmr ($CDCl_3$, 125.8 MHz): 170.91, 135.77, 129.66, 128.85, 128.54, 128.29, 127.92, 67.50, 65.63, 62.63, 14.33.

Example 4



Diethyl 2-phenyl-2-(acetoxymethyl)malonate (**1h**). Diethyl 2-phenyl-2-hydroxymethyl malonate (612 mg; 2.3 mmol) in dry THF (3 ml) was treated with triethylamine (353 µl; 2.53 mmol), acetic anhydride (240 µl, 2.53 mmol) and a few crystals of 4-dimethylaminopyridine. The obtained solution was stirred for 17 h and then poured into ice-water followed by extraction with diethyl ether. The combined organic fractions were washed with saturated aqueous NaCl-solution and dried over $MgSO_4$, filtered and evaporated. After column chromatography on silica gel eluting with benzine (80-100°C) ethyl acetate 3:1 the product was obtained as a yellow oil (340 mg, 47.9%).
^{13}C nmr ($CDCl_3$, 25.8 MHz): 170.62, 168.89, 135.19, 128.72, 128.48, 128.30, 66.28, 62.90, 62.43, 21.14, 14.34.

Example 5



2-Chlorophenylacetonitrile. To a hot (80-90°C) solution of sodium cyanide (2.3 g; 47 mmol) in water (10 ml), a solution of 2-chlorobenzylchloride (4.9 ml; 39 mmol) in absolute ethanol (5 ml) was added dropwise over 20 minutes. The mixture was stirred at reflux for 3 hours. The cooled mixture was diluted with water and excess cyanide was destroyed by addition of potassium permanganate. The mixture was extracted twice with ethyl acetate. The organic phases were washed with brine, dried over magnesium sulphate and concentrated on a rotary evaporator. The residue was

subjected to chromatography on silica gel using a mixture of ethyl acetate and ligroin (1:9 v/v) as the eluent.
Yield: 4.5g (29.8mmol; 76%).

2-(2-Chlorophenyl)butyronitrile. To a solution of 2-chlorophenylacetonitrile (2.1 g; 13.9 mmol) in anhydrous DMF (10 ml), sodium hydride (15.3 mmol; 0.61 g dispersion in mineral oil) was added in portions under a stream of nitrogen. The resulting mixture was stirred at ambient temperature for one hour, and iodoethane (1.2 ml; 14.6 mmol) was added. After additional stirring at ambient temperature for one hour, the mixture was diluted with four volumes of water and extracted twice with ethyl acetate. The extract was dried over magnesium sulphate and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel using a mixture of ethyl acetate and ligroin (1:4 v/v) as the eluent.
Yield: 1.5g (60%).

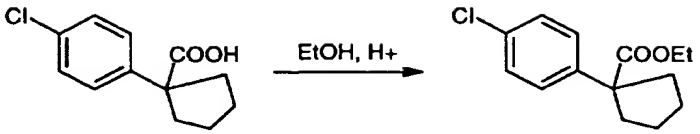
The following compounds were prepared in analogy with the above procedure:

2-(2-Chlorophenyl)-2-ethylbutyronitrile was prepared from 2-(2-chlorophenyl)butyronitrile (1.5 g; 8.4 mmol), sodium hydride (0.37 g 60% in mineral oil) and iodoethane (0.67 ml; 8.4 mmol) in anhydrous DMF (10ml).
Yield: 0.2g (11.5%). M^+ : 207.

2-(3-Phenoxyphenyl)butyronitrile was prepared from 3-phenoxyphenylacetonitril (1.0 g; 4.79 mmol), sodium hydride (4.79 mmol; 0.19 g 60% in mineral oil) and iodoethane (0.38 ml; 4.79 mmol) in anhydrous DMF (10 ml).
Yield: 0.72g (63%).

2-Ethyl-2-(3-phenoxyphenyl)butyronitrile was prepared from 2-(3-phenoxyphenyl)butyronitrile (0.72 g; 3.0 mmol), sodium hydride (3.0 mmol; 0.12 g 60% in mineral oil) and iodoethane (0.24 ml; 3.0 mmol) in anhydrous DMF (10ml).
Yield: 0.32g (40%). M^+: 265.

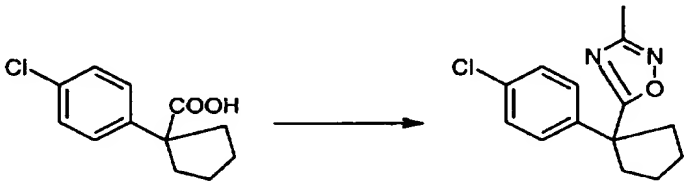
Example 6



Ethyl 1-(4-chlorophenyl)cyclopentane-1-carboxylate. 1-(4-Chlorophenyl)cyclopentane-1-carboxylic acid (0.5 g; 2.22 mmol) was esterified in ethanol (5 ml) with acid catalysis (10 ml conc. hydrochloric acid) under standard conditions.

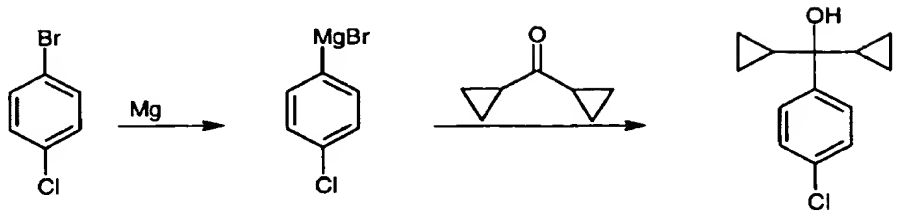
Yield: 0.44g oil (78%). M^+: 252.

Example 7



1-(4-Chlorophenyl)-1-(3-methyl-5-oxadiazolyl)cyclopentane. A stirred solution of 1-(4-chlorophenyl)cyclopentane-1-carboxylic acid (1.0 g; 4.45 mmol) in anhydrous THF (10 ml) was heated to reflux. Carbonyldiimidazole (1.08 g; 6.66 mmol) was added and heating was continued overnight. To this hot solution acetamide oxime (0.82 g; 11.1 mmol) was added and heating was continued an additional night. The resulting mixture was cooled and evaporated to dryness. The residue was partitioned between water and ethyl acetate. The organic phase was dried over magnesium sulphate and concentrated under reduced pressure. The concentrate was suspended in toluene (5 ml), a catalytic amount of p-toluenesulphonic acid was added and the mixture was heated to reflux for three hours. After cooling the mixture was decanted and the oily bottom layer was extracted with toluene. The combined decantate and toluene extract were washed with water, dried over magnesium sulphate and evaporated to dryness. The residue was triturated with ligroin to leave the crystalline product (0.31g; 27%). Mp. 68.7-70.8 °C.

Example 8



Dicyclopropan(4-chlorophenyl)carbinol. A solution of 4-bromo-1-chlorobenzene (3.47 g; 18.15 mmol) in anhydrous diethyl ether (10 ml) was added dropwise to magnesium turnings (0.44 g; 18.15 mmol) covered with anhydrous diethyl ether (10 ml) in an inert atmosphere at a rate that ensured gentle reflux. Following the addition the mixture was refluxed for additionally 30 minutes. To this mixture a solution of diisopropylketone (2.0 g; 18.15 mmol) in anhydrous diethyl ether (10 ml) was added dropwise and the reaction mixture was left at ambient temperature overnight. Ice-cold, diluted hydrochloric acid was added and the product was extracted with diethyl ether. The organic extract was dried over magnesium sulphate, concentrated under reduced pressure and purified by column chromatography on silica gel using a mixture of ethyl acetate and ligroin (1:9 v/v) as the eluent.

This procedure left the pure product (3.3 g; 82%) as an oil. M^+ 222.

Example 9

Electrophysiological Experiments

In this example, the biological activity of the compounds of the invention is demonstrated using electrophysiologic patch-clamp techniques.

Intermediate-conductance Ca^{2+}-activated K^+ channels (IK channels) have been cloned from human placenta and stably expressed in HEK293 cells. The ionic current through the channels is recorded in the whole-cell mode of the patch-clamp technique.

Stable Expression of IK in HEK293 Cells

Human IK (hIK) was excised from pT3T7 (GenBank Acc. No. N56819) using EcoR I and Not I, and sub-cloned into the mammalian expression vector pNS1Z (NeuroSearch), a custom designed derivative of pcDNA3Zeo (InVitrogen), to give the plasmid construct pNS1Z_hIK.

HEK293 tissue culture cells were grown in DMEM (Dulbecco's Modified Eagle Medium) supplemented with 10% FCS (foetal calf serum) at 37°C in 5% CO_2. One day prior to transfection, 10^6 cells were plated in a cell culture T25 flask. The following day, cells were transfected using lipofection (20 µL Lipofectamin™, Life Technologies, with 2.5 µg of the plasmid pNS1Z_hIK in a total volume of 540 µL).

The lipofection mixture was overlaid on the cells and incubated at 37°C for 5 hours. The cells were then rinsed with regular media and grown for 72 hours in DMEM, 10% FCS at 37°C in 5% CO_2.

72 hours post transfection, cells transfected with pNS1Z_hIK were selected in media supplemented with 0.25mg/ml Zeocin. Single clones were picked and propagated in selection media until sufficient cells for freezing were available. Hereafter the cells were cultured in regular medium without selection agent.

Expression of functional hIK channels was verified by patch-clamp measurements.

Whole Cell Recordings

Experiments are carried out on one of several patch-clamp set-ups. Cells plated on coverslips are placed in a 15 µl perfusion chamber (flow rate ~1 ml/min) mounted on a IMT-2 microscope equipped with Nomarski or Hoffmann optics. The microscopes are placed on vibration-free tables in grounded Faraday cages. All experiments are performed at room temperature (20 - 22°C). EPC-9 patch-clamp amplifiers (HEKA-electronics, Lambrect, Germany) are connected to Macintosh computers via ITC16 interfaces. Data are stored directly on the hard disk and analysed by the IGOR software (WaveMetrics, Lake Oswega, USA).

The whole-cell configuration of the patch clamp technique is applied. The tip of a borosilicate pipette (resistance 2-4 MΩ) is gently (remote control system) placed on the cell membrane. Light suction results in a giga seal (pipette resistance increases to more than 1 GΩ) and the cell membrane is then ruptured by more powerful suction. Cell capacitance is electronically compensated and the resistance between the pipette and the cell interior (the series resistance, Rs) is measured and compensated for. Usually the cell capacitance ranges from 5 to 20 pF (depending on cell size) and the series resistance is in the range 3 to 6 MΩ. Rs- as well as

capacitance compensation are updated during the experiments (before each stimulus).

All experiments with drifting Rs-values are discharged. Leak-subtractions are not performed.

Solutions

All compounds of Table 1 were subjected to this experiment.

The extracellular (bath) solution contains: 144 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES (pH = 7.4). Test compounds are dissolved in DMSO from stock solution and then diluted to a final concentration of about 10 µM in the extracellular solution. The concentration of $CaCl_2$ is 7.6 mM and that of $MgCl_2$ is 1.2 mM to give calculated free concentrations of 300 nM and 1 mM, respectively.

Quantification

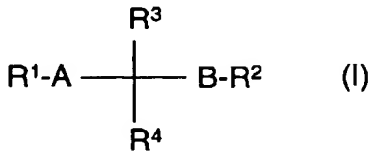
After establishment of the whole-cell configuration, voltage-ramps (usually -100 to +100 mV) are applied to the cell every 5 sec. A stable baseline current is obtained within a period of 100-300 seconds, and the compounds are then added by changing to an extracellular solution containing the compound to be tested. Very little endogenic current (<200 pA at 100 mV, compared to 2-20 nA IK current) are activated under these circumstances in native HEK293 cells.

Results

All compounds tested in this experiment showed activity at a final concentration of about 10 µM, and these compounds therefore are SK/IK/BK channel modulating agents.

CLAIMS

1. A chemical compound represented by the general formula



(I)

and a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

A and B, independently of each another represent

a group of the formula $-(CH_2)_n-$, of the formula $-(CH_2)_n-Y-$ (in either direction), or of the formula $-(CH_2)_n-Y-(CH_2)_m-$;

in which formulas

n and m, independently of each another, represent 0, 1, 2, 3 or 4, and

Y represents O, S, or NR''', wherein R''' represents hydrogen or alkyl;

R^1 and R^2, independently of each another, represent

alkyl, alkenyl, alkynyl, cycloalkyl, amino, trihalogenmethyl, nitro, cyano, or phenyl, or a group of the formula -OR', -SR', -R'OR'', -R'SR'', -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', -C(O)NR'(OR''), -C(S)NR'(OR''), -C(O)NR'(SR''), -C(S)NR'(SR''), $-CH(CN)_2$, $-C(O)NR'_2$, $-C(S)NR'_2$, $-CH[C(O)R']_2$, $-CH[C(S)R']_2$, $-CH[C(O)OR']_2$, $-CH[C(S)OR']_2$, $-CH[C(O)SR']_2$, $-CH[C(S)SR']_2$, CH_2OR', or CH_2SR';

a partially or completely saturated mono- or polycyclic group, a mono- or poly-heterocyclic group, an aralkyl group, or a hetero-alkyl group, which mono- or polycyclic groups or aralkyl or hetero-alkyl groups may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR'', -R'SR'', -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR', or a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -

R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

wherein

R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR"'R"", wherein R"' and R"", independently of each another, represent hydrogen or alkyl;

R^3 and R^4, independently of each another, represent

alkyl, alkenyl, alkynyl, cycloalkyl, amino, trihalogenmethyl, nitro, cyano, or phenyl, or a group of the formula -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', -C(O)NR'(OR"), -C(S)NR'(OR"), -C(O)NR'(SR"), -C(S)NR'(SR"), $-CH(CN)_2$, $-C(O)NR'_2$, $-C(S)NR'_2$, $-CH[C(O)R']_2$, $-CH[C(S)R']_2$, $-CH[C(O)OR']_2$, $-CH[C(S)OR']_2$, $-CH[C(O)SR']_2$, $-CH[C(S)SR']_2$, CH_2OR', or CH_2SR';

wherein

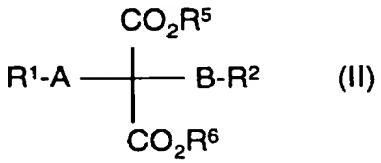
R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR"'R"", wherein R"' and R"", independently of each another, represent hydrogen or alkyl;

or R^3 and R^4 together form a partially or completely saturated mono- or polycyclic group, or a mono- or poly-heterocyclic group, which mono- or polycyclic groups may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR', or a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

wherein

R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR"'R"", wherein R"' and R"", independently of each another, represent hydrogen or alkyl.

2. The chemical compound according to claim 1, which is a malonic acid ester derivative of the general formula



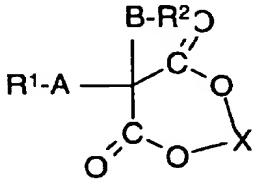
(II)

and a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

A, B, R^1 and R^2 are as defined above, and

R^5 and R^6, independently of each another, represent hydrogen, alkyl, cycloalkyl, or a group of the formula NR"'R"", wherein R"' and R"", independently of each another, represent hydrogen or alkyl.

3. The malonic acid ester derivative of claim 2, in which R^5 and R^6 together form a heterocyclic 6-9 membered ring to give a diester derivative of the general formula



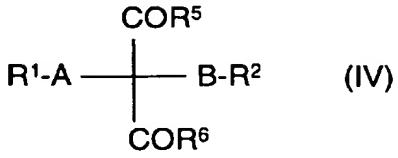
(III)

and a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

A, B, R^1 and R^2 are as defined above, and

X represents a saturated or unsaturated carbon chain of the formula -$(CH_2)_n$-, wherein n is 1, 2, 3 or 4; of the formula -CH_2-CH=CH-CH_2-; of the formula -CH=CH-CH_2-CH_2- (in either direction); or of the formula -CH_2-C≡C-CH_2-.

4. The chemical compound according to claim 1, which is an oxo derivative of the general formula



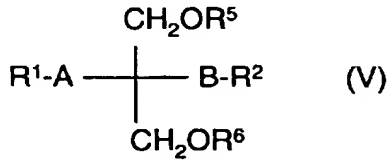
(IV)

and a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

A, B, R^1 and R^2 are as defined above, and

R^5 and R^6, independently of each another, represent hydrogen, alkyl, cycloalkyl, or a group of the formula NR'''R'''', wherein R''' and R'''', independently of each another, represent hydrogen or alkyl.

5. The chemical compound according to claim 1, which is an ether derivative of the general formula



(V)

and a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

A, B, R^1 and R^2 are as defined above, and

R^5 and R^6, independently of each another, represent hydrogen, alkyl, cycloalkyl, or a group of the formula NR'''R'''', wherein R''' and R'''', independently of each another, represent hydrogen or alkyl.

6. The chemical compound according to any of claims 1-5, wherein R^1 and R^2 independently of each another represents an alkyl group; a phenyl or a benzyl group, which phenyl and benzyl groups may optionally be substituted one or

more times with substituent selected from the group consisting of halogen, CF_3, CN, amino or nitro; a mono-heterocyclic group, which heterocyclic group may optionally be substituted one or more times with substituent selected from the group consisting of halogen, CF_3, CN, amino or nitro; a heteroalkyl group, wherein the heterocyclic group a mono-heterocyclic group, which heterocyclic group may optionally be substituted one or more times with substituent selected from the group consisting of halogen, CF_3, CN, amino or nitro.

7. The chemical compound according to claim 6, wherein R^1 and R^2 independently of each another represents phenyl, 1-, 2 or 3-chlorophenyl, 1-, 2- or 3-chlorobenzyl, 1-, 2- or 3-nitrophenyl, 1-, 2- or 3-nitrobenzyl, 1-, 2 or 3-trifluoromethylphenyl, 1-, 2- or 3-trifluoromethylbenzyl, or 1-nitro-3-trifluoromethyl-5-chlorophenyl, 1-nitro-3-trifluoromethyl-5-chlorobenzyl.

8. The chemical compound according to claim 6, wherein the mono-heterocyclic group is an aromatic heterocyclic monocyclic group, in particular 1,3,2,4- or 1,3,4,5-dioxadiazolyl, dioxatriazinyl, dioxazinyl, 1,2,3-, 1,2,4-, 1,3,2- or 1,3,4-dioxazolyl, 1,3,2,4- or 1,3,4,5-dithiadiazolyl, dithiatriazinyl, dithiazinyl, 1,2,3-dithiazolyl, furanyl, furazanyl, imidazolyl, isoimidazolyl, 2-isoimidazolyl, isoindazolyl, isothiazolyl, isoxazolyl, 1,2,3-, 1,2,4-, 1,2,5- or 1,3,4-oxadiazolyl, oxatetrazinyl, oxatriazinyl, 1,2,3,4- or 1,2,3,5-oxatriazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl (azolyl), 1,2,3,4- or 2,1,3,4-tetrazolyl, thiadiazolyl, thiazolyl, thienyl, 1,2,3-, 1,2,4- or 1,3,5-triazinyl, or 1,2,3-, 1,2,4-, 2,1,3- or 4,1,2-triazolyl.

9. The chemical compound according to claim 8, wherein the mono-heterocyclic group is 2-furanyl, 3-furanyl, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isoxazolyl, 1-, 2- or 3-pyridinyl, or 1- or 2-thienyl.

10. The chemical compound according to claim 9, wherein the mono-heterocyclic group is 4-(3,5-dimethyl)-isoxazolyl.

11. The chemical compound according to claim 6, wherein the mono-heterocyclic group is a saturated or partially saturated heterocyclic monocyclic group, in particular 1,3,5,6,2-dioxadiazinyl, 1,2,3,4,5-, 1,2,3,5,4-dioxadiazolyl, dioxanyl, 1,3-dioxolyl, 1,3,5,6,2-dithiadiazinyl, 1,2,3,4,5- or 1,2,3,5,4-dithiadiazolyl, 2-isoimidazolyl, isopyrrolyl, isotetrazolyl, 1,2,3- or 1,2,4-isotriazolyl, morpholinyl, oxadiazinyl, 1,2,4-, 1,2,6-, 1,3,2-, 1,3,6- or 1,4,2-oxazinyl, piperazinyl, piperidinyl, 1,2-, 1,3- or 1,4-pyranyl, or pyrrolidinyl.

12. The chemical compound according to claim 6, wherein the mono-heterocyclic group is an aromatic heterocyclic polycyclic group, in particular acridinyl, benzimidazolyl, 1,2- or 1,4-benzisothiazinyl, 1,2- or 1,4-benzisoxazinyl, benzisoxazole, benzothiazolyl, benzofuranyl, isobenzofuranyl, 2,3-benzopyronyl, 1,2,3,4-benzotetrazinyl, 1,3,4,6-benzotetrazolyl, benzothiazolyl, 1,2,3- or 1,2,4-benzotriazinyl, 1,2,3- or 2,1,3-benzotriazolyl, benzoxadiazolyl, benzoxazolyl, carbazolyl, cinnolinyl, coumarinyl, indazolyl, indolyl, isoindolyl, indolizinyl, purinyl, phenazinyl, phenothiazinyl, phenanthridinyl, phthalazinyl, pteridinyl, quinolinyl, quinoxalinyl, isoquinolinyl, quinazolinyl, quinolizinyl, or xanthrenyl.

13. The chemical compound according to claim 6, wherein the mono-heterocyclic group is a saturated or partially saturated heterocyclic polycyclic group, in particular 1,3-benzisodiazolyl, benzomorpholinyl, 1,2- or 1,4-benzopyranyl, 1,3,2-, 1,4,2-, 2,3,1- or 3,1,4-benzoxazinyl, chromanyl, 4H-chromenyl, or indanyl.

14. The chemical compound according to claim 6, wherein the heteroalkyl group is furfuryl, or picolyl.

15. The chemical compound according to claim 1, wherein the chemical compound is

Diethyl 2-(4-fluorophenyl)-2-(3-picolyl)malonate;

Diethyl 2-(4-nitrophenyl)-2-(2-picolyl)malonate;

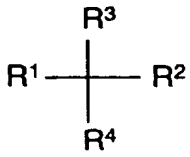
Diethyl 2-(4-nitrophenyl)-2-(4-picolyl)malonate;

Diethyl 2-phenyl-2-(3-picolyl)malonate;

Diethyl 2-(5-chloro-2-nitro-4-(trifluoromethyl)phenyl)-2-(3-picolyl)malonate;

Diethyl 2-benzyl-2-(3-picolyl)malonate;
Diethyl 2-(4-nitrophenyl)-2-[(benzotriazol-1-yl)methyl]malonate;
Diethyl 2-(2-thienyl)-2-(2-picolyl)malonate;
Diethyl 2-(4-(acetylamino)phenyl)-2-(2-picolyl)malonate;
Diethyl 2-(4-(benzoylamino)phenyl)-2-(2-picolyl)malonate; or
2-(4-nitrophenyl)-2-(2-picolyl)malononitril;
or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

16. The chemical compound according to claim 1, represented by the general formula



(VI)

and a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

R^1 and R^2, independently of each another, represent

a partially or completely saturated mono- or polycyclic group, a mono- or poly-heterocyclic group, an aralkyl group, or a hetero-alkyl group, which mono- or polycyclic groups or aralkyl or hetero-alkyl groups may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR', or a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

wherein

R' represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR'"R"", wherein R'" and R'", independently of each another, represent hydrogen or alkyl; and

R^3 and R^4, independently of each another, represent

alkyl, alkenyl, alkynyl, cycloalkyl, amino, trihalogenmethyl, nitro, cyano, or phenyl, or a group of the formula -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', -C(O)NR'(OR"), -C(S)NR'(OR"), -C(O)NR'(SR"), -C(S)NR'(SR"), $-CH(CN)_2$, $-C(O)NR'_2$, $-C(S)NR'_2$, $-CH[C(O)R']_2$, $-CH[C(S)R']_2$, $-CH[C(O)OR']_2$, $-CH[C(S)OR']_2$, $-CH[C(O)SR']_2$, $-CH[C(S)SR']_2$, CH_2OR', or CH_2SR';

wherein

R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR"'R"", wherein R"' and R"", independently of each another, represent hydrogen or alkyl;

or R^3 and R^4 together form a partially or completely saturated mono- or polycyclic group, or a mono- or poly-heterocyclic group, which mono- or polycyclic groups may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR', or a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

wherein

R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR"'R"", wherein R"' and R"", independently of each another, represent hydrogen or alkyl.

17. The chemical compound according to claim 16, wherein

R^1 represents a phenyl group, which may optionally be substituted one or more times with substituents selected from the group consisting of

halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR', or

a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or alkyl;

R^2 represents alkyl, alkenyl, alkynyl, cycloalkyl, amino, trihalogenmethyl, nitro, cyano, or phenyl, or a group of the formula -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', -C(O)NR'(OR"), -C(S)NR'(OR"), -C(O)NR'(SR"), -C(S)NR'(SR"), $-CH(CN)_2$, $-C(O)NR'_2$, $-C(S)NR'_2$, $-CH[C(O)R']_2$, $-CH[C(S)R']_2$, $-CH[C(O)OR']_2$, $-CH[C(S)OR']_2$, $-CH[C(O)SR']_2$, $-CH[C(S)SR']_2$, CH_2OR', or CH_2SR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or alkyl;

R^3 and R^4, independent of each another, represent alkyl, alkenyl, alkynyl, cycloalkyl, amino, trihalogenmethyl, nitro, cyano, or phenyl, or a group of the formula -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', -C(O)NR'(OR"), -C(S)NR'(OR"), -C(O)NR'(SR"), -C(S)NR'(SR"), $-CH(CN)_2$, $-C(O)NR'_2$, $-C(S)NR'_2$, $-CH[C(O)R']_2$, $-CH[C(S)R']_2$, $-CH[C(O)OR']_2$, $-CH[C(S)OR']_2$, $-CH[C(O)SR']_2$, $-CH[C(S)SR']_2$, CH_2OR', or CH_2SR';

wherein

R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or alkyl;

or R^3 and R^4 together form a partially or completely saturated mono- or polycyclic group, or a mono- or poly-heterocyclic group, which mono- or polycyclic groups may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR', or a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, alkenyl, alkynyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -SR', -R'OR", -R'SR", -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', or -C(S)SR';

wherein

R' and R", independently of each another, represent hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or alkoxy, or a group of the formula NR'"R"", wherein R'" and R"", independently of each another, represent hydrogen or alkyl.

18. The chemical compound according to claim 16, wherein

R^1 represents a phenyl group, which may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -R'OR", -C(O)R', -C(O)OR', or

a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -R'OR", -C(O)R', or -C(O)OR';

wherein R' and R", independently of each another, represent hydrogen, or alkyl;

R^2 represents alkyl, cycloalkyl, amino, trihalogenmethyl, nitro, or cyano, or a group of the formula -OR', -R'OR", -C(O)R', -C(O)OR', or CH_2OR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, cycloalkyl or alkoxy;

R^3 and R^4, independent of each another, represent alkyl, cycloalkyl, amino, trihalogenmethyl, nitro, cyano, or phenyl, or a group of the formula -OR', -R'OR", -C(O)R', -C(O)OR', or CH_2OR';

wherein

R' and R", independently of each another, represent hydrogen, alkyl, cycloalkyl or alkoxy.

19. The chemical compound according to claim 16, wherein

R^1 represents

a phenyl group, which may optionally be substituted one or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -R'OR", -C(O)R', -C(O)OR', or

a phenyl or a phenoxy group, which phenyl or phenoxy groups may optionally be substituted on or more times with substituents selected from the group consisting of halogen, trihalogenmethyl, alkyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -R'OR", -C(O)R', or -C(O)OR';

wherein R' and R", independently of each another, represent hydrogen, or alkyl;

R^2 represents alkyl, cycloalkyl, amino, trihalogenmethyl, nitro, or cyano, or a group of the formula -OR', -R'OR", -C(O)R', -C(O)OR', or CH_2OR';

wherein R' and R", independently of each another, represent hydrogen, alkyl, cycloalkyl or alkoxy;

R^3 and R^4 together form a partially or completely saturated mono- or polycyclic group, which mono- or polycyclic groups may optionally be substituted one or more times with substituents selected from the group consisting of

halogen, trihalogenmethyl, alkyl, amino, nitro, cyano, or amido, or a group of the formula -R', -OR', -R'OR", -C(O)R', -C(O)OR';

wherein

R' and R", independently of each another, represent hydrogen, alkyl, cycloalkyl or alkoxy.

20. The chemical compound according to claim 16, which is

2-(3-Phenoxyphenyl)butyronitrile;

2-(2-Chlorophenyl)butyronitrile;

Dicyclopropan(4-chlorophenyl)carbinol;

Ethyl 1-(4-chlorophenyl)cyclopentane-1-carboxylate; or

1-(4-Chlorophenyl)-1-(3-methyl-5-oxadiazolyl)cyclopentane;

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

21. A pharmaceutical composition comprising a chemical compound represented by the general formula (I) of claims 1-20 for the treatment or alleviation of diseases or conditions responsive to modulation of SK_{Ca}, IK_{Ca} and/or BK_{Ca} channels.

22. The pharmaceutical composition according to claim 22, for the treatment or alleviation of respiratory diseases such as asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic hearth disease, angina pectoris, coronary hearth disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.

TITLE: ION CHANNEL MODULATING AGENTS

ABSTRACT

The present invention relates to ion channel modulating agents. More particularly, the present invention relates to a particular class of chemical compounds that has proven useful as modulators of SK_{Ca}, IK_{Ca} and BK_{Ca} channels. In further aspects, the present invention relates to the use of these SK/IK/BK channel modulating agents for the manufacture of medicaments, and pharmaceutical compositions comprising the SK/IK/BK channel modulating agents.

The SK/IK/BK channel modulating agents of the invention are useful for the treatment or alleviation of diseases and conditions associated with the SK/IK/BK channels.